

### **DETAILED ACTION**

Claims 1-26 are currently pending in the instant application.

#### ***Election/Restrictions***

Restriction is required under 35 U.S.C. 121 and 372.

#### ***Lack of Unity Requirement***

This application contains the following inventions or groups of inventions, which are not so linked as to form a single inventive concept under PCT Rule 13.1.

- I. Claims 1-7 drawn to a compound classified in various subclasses of classes 540, 544, 546, 548, and 549.
- II. Claims 8-19 drawn to a method of using a compound of formula (I), classified in various subclasses of classes 540, 544, 546, 548, 549, and 514.
- III. Claims 20-26 drawn to a process of making a compound of formula (I), classified in various subclasses of classes 540, 544, 546, 548, and 549.

Upon thorough consideration of the claims, the examiner has determined that a lack of unity of invention exists, as defined in Rule 13.

PCT Rule 13.1 states that the international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention").

PCT Rule 13.2 states that unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features.

Annex B, Part 1(a), indicates that the application should relate to only one invention, or if there is more than one invention, inclusion is permitted if they are so linked to form a single general inventive concept.

Annex B, Part 1(b), indicates that "special technical features" means those technical features which as a whole define a contribution over the prior art.

Annex B, Part 1(c), further defines independent and dependent claims. Unity of invention only is concerned in relation to independent claims. Dependent claims are defined as a claim which contains all the features of another claim and is in the same category as the other claim. The category of a claim refers to the classification of claims according to subject matter, e.g. product, process, use, apparatus, means, etc.

Annex B, Part 1(f) indicates the "Markush practice" of alternatives in a single claim. Part 1(f(i)) indicates the technical interrelationship and the same or corresponding special technical feature is considered to be met when: (A) all alternatives have a common property or activity, and (B) a common structure is present or all alternatives belong to a recognized class of chemical compounds. Further defining (B) in Annex B, Part 1(f)(i-iii), the common structure must; a) occupy a large portion of their structure, or b) the common structure constitutes a structurally distinctive portion, or c) where the structures are equivalent and therefore a recognized class of chemical compounds, each member could be substituted for one another with the same intended result. That is, with a common or equivalent structure, there is an expectation from knowledge in the art that all members will behave in the same way. Thus, the technical relationship and the corresponding special technical feature result from a common (or equivalent) structure which is responsible for the common activity (or property). Part 1(f(iv)) indicates that when all

alternatives of a Markush grouping can be differently classified, it shall not, taken alone, be considered justification for finding a lack of unity. Part 1(f(v)) indicates that when dealing with alternatives, it can be shown that at least one Markush alternative is not novel over the prior art, the question of unity of invention shall be reconsidered, but does not imply that an objection shall be raised.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted. Again, this list is not exhaustive, as it would be impossible under the time constraints due to the sheer volume of subject matter instantly claimed. Therefore, applicant may choose to elect a single invention by identifying another specific embodiment not listed in the exemplary groups of the invention and examiner will endeavor to group the same.

The claims herein lack unity of invention under PCT rule 13.1 and 13.2 since the compounds defined in the claims lack a significant structural element qualifying as the special technical feature that defines a contribution over the prior art, see U.S. Pat. No. 6,313,312, which teaches a similar class of azabicyclo compounds. Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unit of invention is considered to be proper. Additionally, the vastness of the claimed subject matter, and the complications in understanding the claimed subject matter impose a burden on any examination of the claimed subject matter.

Applicants are advised that the reply to this requirement to be complete must include an election of invention to be examined even though the requirement be traversed (37 CFR 1.143).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Mr. George Heibel on 7/7/2008 a provisional election was made *without traverse* to prosecute the invention of Group I, comprising Claims 1-7 of Formula I depicted in claim 1. Further, an election of species was made of compounds 5 and 6 from claim 6 for search and examination purposes only. Affirmation of this election must be made by applicant in replying to this Office action.

***Priority***

This application is a 371 of PCT/IB03/01367, filed 04/11/2003.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) by application no. PCT/IB02/02663 filed in the International Bureau on 07/08/2002, which papers have been placed of record in the file. The application names an inventor or inventors named in the prior application.

***Information Disclosure Statement***

The information disclosure statement (IDS), filed on 1/19/06, 6/10/08, and 7/30/07 have been considered. Please refer to Applicant's copy of the 1449 submitted herewith.

***Scope of the Elected Invention***

Claims 1-26 are pending in this application. Claims 8-26 are withdrawn from further consideration by the examiner, 37 C.F.R. §1.142(b), as being drawn to a non-elected invention.

The withdrawn subject matter is patentably distinct from the elected subject matter as it differs in structure and element and would require separate search considerations. In addition, a reference, which anticipates one group, would not render obvious the other. The entire scope of claims 1-7 are examined herewith.

***Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification although enabling for a compound of formula, wherein **Ar is aryl, X is no atom, and Y is (CH<sub>2</sub>)<sub>q</sub>, wherein q is 0**, it is not enabled for compounds of formula, wherein **Ar is heteroaryl, X is oxygen, sulphur, NR, and Y is CHR<sub>5</sub>CO or (CH<sub>2</sub>)<sub>q</sub>, wherein q is 1-4**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in MPEP 2164.01(a), “there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.”

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;

3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented (by the inventor);
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary (to make and/or use the invention).

The eight Wands factors are applied to Claims 1-7 of the present invention below:

*(1) The Nature of the Invention*

The nature of the invention is a generic compound of formulae (I)-(V), wherein the fixed core is nitrogen containing aryl ring.

*(2) The Breadth of the claims*

The breadth of the claimed compounds are so broad that one of ordinary skill in the art could not ascertain all the possible combinations and subcombinations that could be made. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, the compounds of formulae (I)-(V) yield an infinite number of combinations that when searched yielded hundreds of hits in STN.

*(3) The state of the prior art*

The state of the prior art is that support for claimed compounds must be found in the disclosure of the application. These class of compounds are already known in the art (See obviousness double patenting rejection below over copending application number 10/525,439.)

*(4) The relative skill of those in the art*

The level of skill in the art (pharmaceutical chemists, physicians) would be high. Only a target range of compounds would be synthesized and it is beyond the scope of one of ordinary skill in the art to have synthesized all of the potential number of compounds claimed.

*(5) The predictability or unpredictability of the art*

The compounds claimed in the instant application, wherein Ar, X and Y can be a number of different combinations include an extremely large scope of the potential compounds rendering the prior art unpredictable for making or using products as claimed on such a grand scale.

A functional group or elemental substitution changes the necessary starting materials for making these compounds as well as the reactivity of said starting materials. The changes in the functional groups result in properties of the compound being changed such as bond length and electronegativity. Therefore based on the unpredictability of the art, it is unknown how to make the claimed compounds.

*(6) The amount of direction or guidance presented (by the inventor)*

The specification in the present invention discloses chemical examples, wherein **Ar is aryl, X is no atom, and Y is (CH<sub>2</sub>)<sub>q</sub>, wherein q is 0.** Based on the guidance in the specification, analogs or derivatives of these compounds can be extrapolated to make the claimed compounds commensurate in scope with the instant claims.

*(7) The presence or absence of working examples*

The specification has working examples of compounds wherein **Ar is aryl, X is no atom, and Y is (CH<sub>2</sub>)<sub>q</sub>, wherein q is 0.** Working examples of additional compounds have not been provided.

*(8) The quantity of experimentation necessary (to make and/or use the invention)*

Given the absence of direction or guidance (or working examples) in the specification for any of the extremely large number of compounds that would be encompassed by the descriptions in claims 1-7, it would cause a skilled artisan an undue amount of experimentation to determine which product the claims were describing. A skilled artisan would not be able to predict if the instantly claimed products could be made or how they would be made because of the lack of guidance in the specification. In addition, a skilled artisan could not predict if the additional combinations would have the same utility as the instantly enabled compounds. Therefore, to overcome this rejection, the scope of the compounds should be defined to those compounds with support in the specification as defined above.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making an **enantiomer, diastereomer and N-oxide** of the claimed compound, does not reasonably provide enablement for making a **solvate, ester, polymorph, or metabolite** of the claimed compound. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention.

*(1) The Nature of the Invention*

The nature of the invention is the compound of formulae (I)-(V), including all pharmaceutically acceptable solvates, ester, enantiomers, diastereomers, N-oxides, polymorphs, or metabolites.



*(2) The Breadth of the claims*

The breadth of the claimed compounds are so broad that one of ordinary skill in the art could not ascertain how to make all solvates, esters, polymorphs, and metabolites of the compounds of formula (I)-(V). The applicable rule for interpreting the claims is that “each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description.” See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, the solvates, esters, polymorphs, and metabolites of compounds of formulae (I)-(V) yield an infinite number of combinations.

*(3) The state of the prior art*

Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in the solid-state as part of an approved drug dosage form (e.g., tablets, capsules, etc.) Solids provide a convenient, compact and generally stable format to store an API or a drug product. Understanding and controlling the solid-state chemistry of APIs, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process.

APIs can exist in a variety of distinct solid forms, including solvates, esters, polymorphs, metabolites, hydrates, salts, co-crystals, and amorphous solids. Each form displays a unique physiochemical property that can profoundly influence the bioavailability, manufacturability, purification, stability and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as solvates, esters, polymorphs, and metabolites are not so common as to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as developmental candidates, it is essential to prepare them, identify conditions for making them and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate supersaturation and promote crystallization. (See Morissette et al., *Advanced Drug Delivery Reviews*, 2004, 56, 275-300.)

The phenomenon of polymorphism, i.e. the crystallization of organic compounds, is of crucial importance to the pharmaceutical industry. Two polymorphs of the same drug molecule may have different physical properties: e.g. solubility, bioavailability, melting points, density, hardness, or color; and may have dramatically different properties that affect the scale-up process. Due to the differences between polymorphs, the drug regulatory authorities (e.g. the FDA) are increasingly demanding more information about potential drug products before granting approval. The conditions under which polymorphs interconvert is also of crucial importance, particularly when drugs may encounter exposure to changes in temperature, pressure, and relative humidity during processes such as drying, granulation, milling, compression, and storage. Therefore, for these reasons, the state of the prior art is one of unpredictability. The science of crystallization has evolved such that said differences in properties implies patentable distinctiveness between polymorphs.

*(4) The relative skill of those in the art*

The level of skill in the art (pharmaceutical chemists, physicians) would be high. Only a target range of APIs would be synthesized and it is beyond the scope of one of ordinary skill in the art to have synthesized all of the potential number of APIs claimed.

*(5) The predictability or unpredictability of the art*

The APIs claimed in the instant application, wherein it is in solvate, ester, polymorph, or metabolite form yield an extremely large scope of potential targets rendering the prior art unpredictable for making or using products as claimed on such a grand scale.

*(6) The amount of direction or guidance presented (by the inventor)*

The specification in the present invention does not provide direction or guidance for making the solvate, ester, polymorph, or metabolite form of the compound.

*(7) The presence or absence of working examples*

The specification does not have working examples of the solvate, ester, polymorph, or metabolite form of the compound.

*(8) The quantity of experimentation necessary (to make and/or use the invention)*

Given the absence of direction or guidance (or working examples) in the specification for any of the extremely large number of compounds that would be encompassed by the terms the solvate, ester, polymorph, or metabolite, it would cause a skilled artisan an undue amount of experimentation to determine which product the claims were describing. A skilled artisan would not be able to predict if the instantly claimed products could be made or how they would be made because of the lack of guidance in the specification. In addition, a skilled artisan could not predict if the additional combinations would have the same utility as the instantly enabled

compounds. Therefore, to overcome this rejection, the scope of the compounds should be defined to those compounds with support in the specification as defined above.

MPEP 2164.01(a) states, “[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular compound is, in fact, a solvate, ester, polymorph or metabolite.

***Claim Rejections - 35 USC § 112, 2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms “enantiomers,” “diastereomers,” “N-oxides,” “salts,” “carriers,” “excipients,” and “dilutents” render the claim confusing because one skilled in the art would not know if the salt form of the compound would have to be present in conjunction with the compound itself. It is suggested that the singular form be adopted, such as “enantiomer,” “diastereomer,” “N-oxide,” “salt,” “carrier,” “excipient,” and “diluent”.

***Obviousness Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

Art Unit: 1626

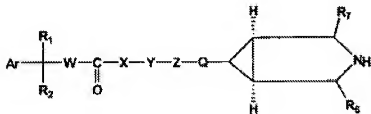
improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

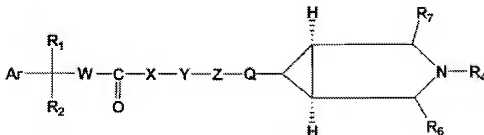
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-6 of US Pat No 7,288,562 ('562 Pat).

Instant claim 1 (filing or 371(c) date: 1/19/06) claims a compound of formula (I)



The '562 Pat claim 1 (filing or 371(c) date: 8/1/05) a compound of formula (I)



The difference between the '562 Pat and the instant claims is that in the instant claims the nitrogen on the ring is hydrogen substituted, while in the '562 Pat it is substituted with a R<sub>4</sub> moiety, wherein the R<sub>4</sub> moiety is methyl, alkyl, optionally further substituted with halogen, etc....

Although the conflicting claims are not identical, they are not patentably distinct from each other because one of ordinary skill in the art would recognize that structural variations are obvious in view of the state of the art.

It is well known in the art that substituting hydrogen for methyl and vice versa is obvious. Hydrogen and methyl are deemed obvious variants. In re Wood, 199 USPQ 137.

It is well known in the art that substitution with well known bioisosteres is obvious. Bioisosteres of compounds are well known in the art. See Patani et al., Chem Rev, 1996, Vol. 96 (8), pp. 3147-3176, especially page 3170. Patani teaches that common bioisosteres include halogen v. hydrogen replacement; hydroxyl v. amine replacement; and so on. Patani et al, page 3147 and 3150.

It is well known in the art that homologs are obvious. Compounds which are homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -

CH<sub>2</sub>- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). See MPEP 2144.09(II).

Prior art structures do not have to be true homologs to render structurally similar compounds *prima facie* obvious. In re Payne, 606 F.2d 303, 203 USPQ 245 (CCPA 1979) (Claimed and prior art compounds were both directed to heterocyclic carbamoyloximino compounds having pesticidal activity. The only structural difference between the claimed and prior art compounds was that the ring structures of the claimed compounds had two carbon atoms between two sulfur atoms whereas the prior art ring structures had either one or three carbon atoms between two sulfur atoms. The court held that although the prior art compounds were not true homologs of the claimed compounds, the similarity between the chemical structures and properties is sufficiently close that one of ordinary skill in the art would have been motivated to make the claimed compounds in searching for new pesticides.). See MPEP 2144.09 (III).

In addition, they are not patentably distinct from each other because one of ordinary skill in the art would recognize that the C1-C15 saturated or unsaturated aliphatic hydrocarbon group optionally substituted is an obvious variation based on the disclosure of the '562 Pat. The '562 Pat teaches the method of making the compounds with and without the R<sub>4</sub> moiety and one of ordinary skill in the art would know that the process disclosed in the '562 Pat could be used to make the instantly claimed compounds and the process disclosed in the instant application could be used to make the '562 Pat compounds.

The instant obviousness rejection is based on the close structural similarity of the instantly claimed compounds to the prior filed application compounds and the common utility shared among the compounds. There is an expectation among those of ordinary skill in the art that similar structural compounds will have similar properties and that modification of a known structure is mere experimentation within the means of a skilled artisan. See MPEP 2144.09(I). Therefore, claims 1-7 are rejected as obvious over the prior art.

***Telephone Inquiry***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susannah Chung, Esq. whose telephone number is (571) 272-6098. The examiner can normally be reached on M-F, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Art Unit: 1626

/Susannah Chung/ Esq.

July 29, 2008

/Joseph K. McKane/

Supervisory Patent Examiner, Art Unit 1626